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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
08/894,246	05/22/98	PERRICAUDET	M EX95001-US

EXAMINER	
CHEN, S	
ART UNIT	**PAPER NUMBER**
1633	19

029693
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DATE MAILED: 07/30/01

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary	Application No. 08/894,246	Applicant(s) PERRICAUDET ET AL.	
	Examiner Shin-Lin Chen	Art Unit 1633	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *29 May 2001* .

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *26-64* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *26-64* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Applicants' amendment filed 5-29-01 has been entered. Claims 26-64 are pending and under consideration.

Claim Objections

Applicants indicate that the language in claim 40 has not been amended since it is originally presented in the preliminary amendment of August 14, 1997. Therefore, the mention of amendment of claim 40 in the amendment filed 8-24-00 (Paper No. 14) is considered moot. The objection of claim 40 has been withdrawn.

Claim Rejections - 35 USC § 112

1. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

2. Claims 61-64 remain rejected under 35 U.S.C. 112, second paragraph, as being incomplete for omitting essential steps, such omission amounting to a gap between the steps. See M.E.P.. § 2172.01. The omitted steps are: for example, whether the survival of the cell has been prolonged. Applicant's arguments filed 5-29-01 have been fully considered but they are not persuasive.

Applicants argue that the preamble indicates "prolonging the survival" and the "detecting the presence of mRNA or protein expressed" would detect a state of the cell and its survival (amendment, page 3 first paragraph). This is not found persuasive because the preamble "prolonging the survival" only indicates the purpose of the claimed method but fails to indicate whether the survival of the cell has been prolonged. Similarly, "detecting the presence of mRNA or protein expressed" also fails to indicate whether the survival of the cell has been prolonged. Thus, the claims remain rejected for the reasons set forth above and the reasons of record.

Claim Rejections - 35 USC § 112

3. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

4. Claims 26-64 remain rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of decreasing CD4+, CD3+ and CD8+ T cells by the combination of anti-CD3 or anti-CD4 antibody with Ad-βgal-gp19K expressing gp19K protein of adenovirus, decreasing cytotoxic activity of splenocytes, isolated from animals treated with anti-CD4 antibody and Ad-βgal-gp19K, on p815-β-gal target cells expressing β-galactosidase, and prolonging the expression of β-gal in a liver of a mouse with the combination

of anti-CD4 antibody and Ad-βgal-gp19K, does not reasonably provide enablement for a composition comprising any immunosuppressive agent and a recombinant adenovirus containing a therapeutic gene and any immunoprotective gene such as ICP47 gene and UL18 gene, and a method for expression of a therapeutic gene using said composition. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims. Applicant's arguments filed 5-29-01 have been fully considered but they are not persuasive.

Applicants argue that "There does not seem to be any discuss of inoperative combinations in the Office Action" and "even some particular number of combinations, does not compel a conclusion of non-enablement. Some evidence of non-enabling species or some reasons to doubt applicants' assertions must be presented" (reply, bridging page 3-4). This is not found persuasive because of the reasons of record. As discussed in the preceding Official actions, the claims read on gene therapy in light of the specification which indicates that the present application is to provide a novel method for prolonging gene, e.g. therapeutic gene, expression in a gene therapy using adenovirus vector *in vivo*. The state of the prior art for gene therapy was not well developed and was highly unpredictable at the time of the invention. There are numerous factors that contribute to gene transfer efficiency do complicate the gene therapy art which have not been shown to be overcome by routine experimentation. Further, Linsley suggests that virtually complete suppression (>95%) of *in vivo* immune responses by CTLA4Ig does not necessarily lead to tolerance (e.g. abstract, page 794). The level of immunoprotective effect of a

immunoprotective gene such as a gp19K, a ICP47, a UL18 gene and other unidentified immunoprotective genes may vary because of different mechanisms of their immunoprotective function. Kay et al., 1997 (PE) reports that although recombinant adenovirus vectors offer a very efficient means by which to transfer genetic information into cells *in vivo*, antigen-dependent immunity limits the duration of gene expression and prevents retreatment (e.g. abstract). Therefore, the effectiveness to create a permissive immune environment and to induce a state of tolerance with regard to predefined foreign antigen depends on the potency of the antigen, the immunosuppressive agent and the immunoprotective gene used. A skilled person in the art would have to trial and error to determine which combination of an immunosuppressive agent and a immunoprotective gene would exhibit immunoprotective effect on the treated subject and prolong the expression of a gene of interest, such as a therapeutic gene, in said subject.

Applicants argue that previously submitted evidence supports the enablement of the claims (response to Paper No. 13 and the papers submitted and discussed) (amendment, page 4, second paragraph). This is not found persuasive because of the reasons set forth above and the reasons of record. Linsley and Kay indicates the dose of antibody and the type of antigen play a role in the suppression of *in vivo* immune response. Their teachings implicate unpredictability of the effectiveness to create a permissive immune environment and to induce a state of tolerance with regard to predefined foreign antigen. The Poller reference submitted in previous amendment filed 8-24-00 (Paper No. 14) has been addressed in preceding Official action mailed 12-26-00 (Paper No. 16).

Applicants argue that the claims are not limited to therapeutic applications for gene therapy in humans, and if other uses are enabled, the claims have been properly enabled. This is not found persuasive because of reasons of record and the reasons set forth above. Further, although the claims are not limited to therapeutic application of gene therapy, the claims do encompass therapeutic applications of gene therapy *in vivo* that is not enabled because of the unpredictability of the art and the broad scope encompassed by the claims. The application implies no other use for the claimed invention. Applicants do not point out any "other enabled uses" in their argument.

Applicants argue that the factors cited by Verma and Eck are not relevant to the issues the Patent Office reviews and further cited *In re Brana* case law (amendment, page 4-5). This is not found persuasive because of the reasons set forth above and the reasons of record. Although it is not necessarily to enable human clinical trials, the claimed invention must be enabled by the specification disclosed. The factors cited by Eck contribute to gene transfer efficiency for a successful gene therapy *in vivo* and they do complicate the gene therapy art which have not been shown to be overcome by routine experimentation. These factors are relevant to the enablement of the claimed invention of the present application. Further, the chemical compound cited in *In re Brana* is different from the vector and genetic materials used in gene therapy. The art of chemical compound having pharmaceutical properties differ dramatically from the art of gene therapy. Thus, the statement cited in *In re Brana* could not be applied to the art of gene therapy *in vivo*.

Applicants argue that the Office fails to provide sufficient evidence to support its assertions of non-enablement and no evidence that applicants' statement concerning enablement are incredible (amendment, bridging page 5-6). This is not found persuasive because of the reasons set forth above and the reasons of record. Further, the Office does not state that "applicants' statement concerning enablement are incredible", the Office only indicates that the claimed invention is not enabled in light of the disclosure of the specification and the post-filing papers submitted.

Conclusion

No claim is allowed.

5. **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event,

however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Shin-Lin Chen whose telephone number is (703) 305-1678. The examiner can normally be reached on Monday to Friday from 9 am to 5:30 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Deborah Clark can be reached on (703) 305-4051. The fax phone number for this group is (703) 308-4242.

Questions of formal matters can be directed to the patent analyst, Kimberly Davis, whose telephone number is (703) 305-3015.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist, whose telephone number is (703) 308-0196.

Shin-Lin Chen, Ph.D.

Deborah Clark

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